AF/GP 1648 $

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Our Ref: 1038-384 MIS:as

In re patent application

No. 08/286,189

Applicant: Sonia E. Sanhueza et al

Title: INACTIVATED RESPIRATORY SYNCYTIAL VIRAL VACCINES

Filed: August 5, 1994

Group No. 1817

Examiner: K. Masood

March 11, 1999

APPEAL BRIEF

BY COURIER

The Commissioner of Patents
and Trademarks,
BOX AF,
Washington, D.C. 20231,
U.S.A.

Dear Sir:

1. Introduction

This Appeal Brief is submitted pursuant to the Examiner's final rejection of claims 1, 3 to 9 and 11 to 16. Three copies of this Appeal Brief are being submitted. The Appeal Brief fee is included in the enclosed cheque.

2. Request for Extension of Time

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of five months of the period for filing this Appeal Brief. The prescribed fee is included in the enclosed cheque.

3. Real Party in Interest

The real party in interest is Connaught Laboratories Limited of 1755 Steeles Avenue West, North York, Ontario, Canada, M2R 3T4 by virtue of an Assignment from the inventors registered September 29, 1994 under Reel/Frame 7150/0232.

4. Related Appeals and Interferences

The applicants had filed an Appeal from the Final Rejection of claims 17 to 19 of copending Application No. 08/472,174, an application of which this application is the

parent. Claims 17 to 19 were deleted from this application as a result of a restriction requirement. The Examiner has issued a new final rejection on Application No. 08/472,174, so that the claims thereof are not currently on appeal. Application No. 08/583,124, related to this application, contains method claims similar to but differing in scope from those in this application, also is on Appeal. The decision in that appeal will directly affect or have a bearing on the appeal in this application. The appellant, the appellant's legal representative and assignee are unaware of any additional appeals or any interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

5. Status of Claims

The application was filed with 19 claims as a continuation-in-part of Application No. 08/102,742 (now abandoned). As a result of a restriction requirement, claims 17 to 19 were withdrawn from consideration and deleted from the application. Claims 2 and 10 have been cancelled by Amendment. Claims 1, 3 to 9, and 11 to 16 are pending. The form of the claims appealed appears in the Appendix hereto.

6. Status of All Amendments filed Subsequent to Final Rejection

A first Office Action was received on this application dated October 5, 1995 and an Amendment was submitted responsive to this Office Action on April 4, 1996. A second Office Action dated July 12, 1996 issued. A response to this Office Action was filed October 3, 1996.

A third Office Action dated November 26, 1996 issued. This latter Office Action contained no notation or other indication that the Action was Final. The third Office Action indicated withdrawal of rejections of claims 1 to 16 under 35 USC 112, first paragraph, but stated:

> "Claims 1 to 16 remain rejected under 35 USC 103 for the reasons presented at pages 7 to 15 of the Office Action 7/12/96.
>
> Applicants arguments filed 10/3/96 have been considered but have not been found persuasive."

Accordingly, the claims were rejected a second time on the same ground. It is not known why the third Office Action was not made final under these circumstances. However, 37 CFR 1.191(a) permits an Appeal to be lodged from a second rejection of the claims on the

same ground, even though non-Final and applicants Notice of Appeal was filed pursuant to that Rule (even though the Notice of Appeal and does not specifically refer to 37 CFR 1.191(a)).

An Amendment was forwarded to the PTO by courier on April 23, 1997 and was presumably filed the following day. The form of the claims presented in the Appendix is that following the Amendment of April 23, 1997.

Pursuant to the Notice of Appeal, an Appeal Brief was submitted. Subsequently, a Final Office Action was received dated February 13, 1998 in which the Examiner stated:

> "Applicant has prematurely filed the Notice of Appeal and the Appeal Brief without allowing the re-examination to take place. Furthermore, the Brief includes the amended claims submitted in the April 23, 1997 amendment, which claims, by virtue of the amendments have never been examined and therefore can not now be appealed."

Since the claims had been rejected a second time, although non-final, an Appeal with Appeal Brief was an appropriate course of action under 35 CFR 1.171(a).

Nevertheless, the Final Action of February 13, 1998 noted that:

> "All previous rejections have been withdrawn in view of the amendments to the claims."

In their place, the Examiner entered a new ground of rejection, under 35 USC 112, first paragraph, the subject of this appeal. A Request for Reconsideration was forwarded to the Office on June 8, 1998, pointing out that the issues raised had also been raised in an Office Action of October 5, **1995**, applicants had submitted arguments in response thereto and that, in the subsequent Office Action of November 26, 1996, the rejection had been withdrawn. No response has been received to the Request for Reconsideration.

7. Concise Summary of the Invention

The present invention relates to immunology and, in particular, the provision of a vaccine against infection caused by respiratory syncytial virus. The invention involves a vaccine composition capable of producing a respiratory syncytial (RS) virus specific protective immune response in a human host immunized therewith, comprising a purified inactivated RS viral preparation which is free from cellular and serum components and which is non-infectious, non-immunopotentiating, immunogenic and protective, and a carrier therefor (page 5, lines 13 to 28; claims 1, 3 and 4). An inactivated RS viral vaccine

composition which is protective and non-immunopotentiating has not previously been described.

The invention further includes a method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, comprising a plurality of steps. The RS virus is grown on a continuous cell line of vaccine quality. The grown virus is harvested and the harvested virus is purified under non-denaturing conditions to produce a purified virus free from cellular and serum components. The purified virus then is inactivated with an inactivating agent to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, which then is formulated as a vaccine (page 4, lines 20 to 32; claims 5 to 9, and 11 to 14). In this procedure, the RS virus first is purified and then inactivated. This procedure is the key to providing a non-immunopotentiating composition.

The invention additionally includes a method of immunizing a host against disease caused by respiratory syncytial virus by administering to the host an effective amount of the vaccine composition. (page 5, line 29 to page 6, line 1; claims 15, 16).

8. Concise Statement of All Issues Presented for Review

The following issue is presented for review:

- claims 1, 3 to 9 and 11 to 16 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. Grouping of Claims for Each Ground of Rejection which Applicant Contests

The claims do not stand or fall together, but individual claims represent independently patentable subject matter, as outlined below.

10. Argument

(a) Background

Human respiratory syncytial (RS) virus is the main cause of lower respiratory tract infections among infants and young children. Globally, 65 million infections occur every year resulting in 160,000 deaths. In the USA alone, 100,000 children may require hospitalization for pneumonia and bronchiolitis caused by RS virus in a single year. Providing inpatient and ambulatory care for children with RS virus infections costs in excess of $340 million annually in the USA. Severe lower respiratory tract disease due to RS virus infection

predominantly occurs in infants two to six months of age. Approximately 4,000 infants in the USA die each year from complications arising from severe respiratory tract disease caused by infection with RS virus and Parainfluenza type 3 virus (PIV-3). The World Health Organization (WHO) and the National Institute of Allergy and Infectious Disease (NIAID) vaccine advisory committees have ranked RS virus second only to HIV for vaccine development.

RS virus is a member of the *Paramyxoviridae* family of the pneumovirus genus. The two major protective antigens are the envelope fusion (F) and attachment (G) glycoproteins. The F protein is synthesized as a 68 kDa precursor molecule (FO) which is proteolytically cleaved into disulfide-linked Fl (48 kDa) and F2 (2O kDa) polypeptide fragments. The G protein (33 kDa) is heavily O-glycosylated giving rise to a glycoprotein of apparent molecular weight of 90 kDa. Two broad subtypes of RS virus have been defined: A and B. The major antigenic differences between these subtypes are found in the G glycoprotein.

A safe and effective RS virus vaccine is not available and is urgently needed. Approaches to the development of RS virus vaccines have included inactivation of the virus with formaldehyde, isolation of cold-adapted and/or temperature-sensitive mutant viruses and isolation of the protective antigens of the virus. Clinical trial results have shown that both live attenuated and formalin-inactivated vaccines failed to adequately protect vaccinees against RS virus infection. Problems encountered with cold-adapted and/or temperature-sensitive RS virus mutants administered intranasally included clinical morbidity, genetic instability and overattenuation.

A live RS virus vaccine administered subcutaneously also was not efficacious. Inactivated RS viral vaccines have typically been prepared using formaldehyde as the inactivating agent. Data has been reported on the immune response in infants and children immunized with formalin-inactivated RS virus. Infants (2 to 6 months of age) developed a high titre of antibodies to the F glycoprotein but had a poor response to the G protein. Older individuals (7 to 40 months of age) developed titres of F and G antibodies comparable to those in children who were infected with RS virus. However, both infants and children developed a lower level of neutralizing antibodies than did individuals of comparable age with natural RS virus infections. The unbalanced immune response, with high titres of antibodies to the main immunogenic RS virus proteins F (fusion) and G (attachment) proteins but a low neutralizing antibody titre, may be in part due to alterations of important epitopes in the F and G glycoproteins by the formalin treatment.

Furthermore, some infants who received the formalin-inactivated RS virus vaccine developed a more serious lower respiratory tract disease following subsequent exposure to natural RS virus than did non-immunized individuals. The formalin-inactivated RS virus vaccines, therefore, have been deemed unacceptable for human use.

Evidence of an aberrant immune response also was seen in cotton rats immunized with formalin-inactivated RS virus. Furthermore, evaluation of RS virus formalin-inactivated vaccine in cotton rats also showed that upon live virus challenge, immunized animals developed enhanced pulmonary histopathology.

The mechanism of disease potentiation caused by formalin-inactivated RS virus vaccine preparations remains to be defined but is a major obstacle in the development of an effective RS virus vaccine. The potentiation may be partly due to the action of formalin on the F and G glycoproteins. Additionally, a non-RS virus specific mechanism of disease potentiation has been suggested, in which an immunological response to contaminating cellular or serum components present in the vaccine preparation could contribute, in part, to the exacerbated disease. Indeed, mice and cotton rats vaccinated with a lysate of HEp-2 cells and challenged with RS virus grown on HEp-2 cells developed a heightened pulmonary inflammatory response.

Furthermore, RS virus glycoproteins purified by immunoaffinity chromatography using elution at acid pH were immunogenic and protective but also induced immunopotentiation in cotton rats.

There clearly remains a need for immunogenic preparations, including vaccines, which are not only effective in conferring protection against disease caused by RS virus but also does not produce unwanted side-effects, such as immunopotentiation.

Art recognized approaches to the developments of RSV vaccines have been summarized in recent review articles, none of which propose the development of an inactivated RSV vaccine. Such review articles are of record in this application (submitted with April 4, 1996 Amendment).

Accordingly, for many years, the production of an RS virus vaccine has been hampered by the adverse effects produced with a formalin-inactivated RS virus in a human clinical trial conducted in the United States in the 1960's. In view of these results, the efforts of vaccine producers in the last 30 years have concentrated on the production of live attenuated RS virus mutants or subunit vaccines, rather than the use of inactivation. The

various review articles of record herein relating to the RS virus quite clearly demonstrate that no consideration is being given by the at to the inactivation of virus for providing an RS virus vaccine. There is a clear prejudice in the art against using such procedure for the preparation of RS virus vaccine.

(b) Nature of the Invention

The applicants have found that, if the virus first is purified and then inactivated using β-propiolactone, ascorbic acid or octyl glycopyranoside, then a safe and effective vaccine preparation can be obtained which, in particular, elicits a protective immune response without causing enhanced pulmonary pathology (immunopotentiation). It is submitted that this procedure, the vaccine formed thereby and the method of immunization using the vaccines are fully enabled by the specification.

(c) Rejection under 35 USC 112, first paragraph

As noted above, this ground of rejection was introduced in the Final Action after having been specifically withdrawn in a prior Office Action. In the Final Action, the Examiner states:

> "The specification shows inactivated RSV, which has been inactivated by n-octyl-β-D-glucopyranoside, β-propiolactone, or ascorbic acid, and which elicits antibody production in cotton rats."

and:

> "The specification provides no probative evidence to support the claimed vaccine which would protect humans against RSV. In order to enable claims to drugs and their uses, either *in vivo* or *in vitro* data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the at that the claims are sufficiently enabled. When the claims are directed to humans adequate animal data would be acceptable in those instances wherein one of ordinary skill in the at would accept the correlation to humans. Thus in order to rely on animal data there must exist an art-recognized animal model for testing purposes."

Following a highly selective discussion of the literature, the Examiner concludes in the Final Action that:

> "Therefore, it appears that the cotton rat data does not correlate to humans and the cotton rat is not an art accepted model for vaccine evaluation with regards to RSV in humans and particularly infants."

While the Examiner characterizes the rejection as a new one, as pointed out above, precisely the same issue arose in the Office Action of October 5, 1995, when the Examiner stated:

> "... protection observed in the cotton rat model cannot be extrapolated to humans. Due to the unpredictability of RSV vaccines to provide protection in humans, it would require undue experimentation to determine how to use the claimed vaccine compositions to provide protection in humans."

The applicants submitted considerable arguments with respect to this rejection, which ultimately resulted in withdrawal of the rejection. In view of the Examiner now restating the rejection, it would appear that it will be necessary, again, to set forth such arguments, which, it is submitted, is unduly burdensome to the applicants, particularly in the absence of any explanation by the Examiner for, once more, advancing a ground of rejection previously specifically withdrawn.

As noted above, the Examiner's conclusion in the Final Action is that:

> "Therefore, it appears that the cotton rat data does not correlate to humans and the cotton rat is not an art accepted model for vaccine evaluation with regards to RSV in humans and particularly infants."

It is submitted for the following reasons, that the Examiner is in error, and that the cotton rat is a model of human efficacy for infections by RSV.

The applicants have clearly shown protection in the accepted animal model of the RSV infection, namely the cotton rat. Whether or not the effectiveness of the vaccine based on results achieved in the cotton rat model may not necessarily be extrapolated to humans is immaterial, if the cotton rat model is an accepted animal model of the infection.

In any event, there is a direct correlation between antibody titres in the sera of cotton rats which inhibit significant pulmonary resistance to RSV infection and infants younger than two months of age who exhibit relative resistance to serious RSV respiratory tract disease. These resistant infants have passively acquired RSV serum neutralizing antibodies of the same mean titres (1:200 to 1:300) as cotton rats, as described by the Chanock reference, to which the Examiner refers. It is clear, therefore, that an immunogen which produces an appropriate titre of neutralizing antibodies in cotton rats provides a prediction of protection in humans by that immunogen.

The Examiner's attention is also directed to Murphy et al, WO 93/21310 which states:

> "... the cotton rat appears to be a reliable experimental surrogate for the response of infected monkeys and humans to immunotherapy with RSV neutralizing antibodies. For example, the amount of RSV neutralizing antibodies associated which a therapeutic effect in cotton rats as measured by the level of such antibodies in the serum of treated animals (i.e., serum RSV neutralizing titre of 1:320 to 1:518) is in the same range as that demonstrated for monkeys (i.e., 1:877). A therapeutic effect in cotton rats was manifested by a one hundred fold or greater reduction in virus titer in the lung (Price et al, J. Virol., 61:1851-1854) while in monkeys a therapeutic effect was observed to be a 50-fold reduction in pulmonary virus titre (Hemming et al, J. Infect. Dis., 152:1083-1087 (1985)." (page 9, line 21 to page 10, line 21).

> Murphy et al conclude:
>
> "Based on these studies, it would appear that the cotton rat constitutes a relevant model for predicting the success of an RSV vaccine in infants and small children." (page 10, lines 16 to 18).

Accordingly, despite the comments of the Examiner, those skilled in the art consider the cotton rat to be the relevant model for predicting the success of an RSV vaccine is useful in infants and small children. Accordingly, applicant's data, as presented in the application, can be extrapolated to humans.

Further, Prince et al (J. Virol. 55; 517; Virus Res. 3; 193) found that administration of RSV-specific neutralizing antibodies could not only prevent RSV infection in the lungs of infant cotton rats when administered prior to virus exposure, but also rapidly resolved infection when given at the height of infection. Crowe et al. (PNAS 91; 1386) has stated that:

> "Clinical trials have validated these aforementioned experimental observations." (col. 2, page 1386).

Groothuis et al (N. Engl. J. Med. 329:1524) have reported that:

> "Administration of high doses of RSV immune globulin is a safe and effective means of preventing lower respiratory tract infection in infants and young children at high risk for this disease." (see col. 2; abstract).

Accordingly, the results obtained in cotton rats were supported by data obtained in human trials.

Results from a recent clinical trial which evaluated the safety and immunogenicity of an RSV subunit vaccine provides additional evidence that the data obtained in cotton rats has clinical relevance. An immunoaffinity-purified F protein

preparation was highly immunogenic and protected cotton rats against live virus challenge (Walsh et al, J. Infec. Dis., 155; 1198). This subunit preparation was also proved to be safe and immunogenic in seropositive toddlers (Paradiso et al., Pediatr. Infect. Dis. J. 13; 792).

Based upon this data, it is clear that the results obtained in cotton rats have clinical relevance. Accordingly, even if the Examiner's objection to the specification was properly made, there is no basis for asserting that it would require undue experimentation to determine how to use the claimed vaccine compositions to provide protection in humans.

Having regard to the above, it is submitted that the claims fully comply with the provisions of 35 USC 112, first paragraph and the rejection should be reversed.

11. Summary

It will be seen from the discussion above that all applicants pending claims are enabled and hence the rejection of the claims under 35 USC 112, first paragraph, should be reversed.

Respectfully submitted,

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APPENDIX

CLAIMS APPEALED

1. A vaccine composition capable of producing a respiratory syncytial (RS) virus specific protective immune response in a human host immunized therewith, comprising a purified, inactivated RS viral preparation which is free from cellular and serum components and which is non-infectious, non-immunopotentiating, immunogenic and protective, and a carrier therefor.

3. The composition of claim 1 wherein said carrier further comprises an adjuvant.

4. The composition of claim 1 formulated to be administered in an injectable form, intranasally, orally, or to mucosal surfaces.

5. A method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, which comprises:

growing RS virus on a continuous cell line of vaccine quality to produce a grown virus;

harvesting said grown virus to produce a harvested virus;

purifying said harvested virus under non-denaturing conditions to produce a purified virus free from cellular and serum components;

inactivating said purified virus with an inactivating agent to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

6. The method of claim 5 wherein said inactivating agent is β-propiolactone.

7. The method of claim 5 wherein said inactivating agent is a non-ionic detergent.

8. The method of claim 7 wherein said non-ionic detergent is selected from the group consisting of n-octyl-α-D-glucopyranoside and n-octyl-β-D-glucopyranoside.

9. The method of claim 5 wherein said inactivating agent is ascorbic acid.

11. The method of claim 5 wherein said continuous cell line is a VERO cell line.

12. A method of preparing a non-immunopotentiating vaccine capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, which comprises:

growing RS virus on a continuous cell line of vaccine quality to produce a grown virus;

harvesting said growth virus to produce a harvested virus;

purifying said harvested virus under non-denaturing conditions to produce a purified virus substantially free from cellular and serum components by:

(i) microfiltration to remove cell debris,

(ii) tangential flow ultrafiltration to remove serum components and provide a retentate,

(iii) pelleting the retentate by ultracentrifugation to further remove serum components, and

(vi) subjecting the pelleted material to sucrose density gradient centrifugation;

inactivating said purified virus with an inactivating agent selected from the group consisting of β-propiolactone, a non-ionic detergent which is n-octyl-α-D-glucopyranoside or n-octyl-β-D-glucopyranoside, and ascorbic acid, to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

13. The method of claim 12 wherein said tangential flow ultrafiltration is effected by employing an about 100 to about 300 kDa nominal molecular weight cutoff membrane.

14. A method of preparing a non-immunopotentiating vaccine capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, which comprises:

growing RS virus on a continuous cell line of vaccine quality to produce a grown virus;

harvesting said growth virus to produce a harvested virus;

purifying said harvested virus under non-denaturing conditions to produce a purified virus substantially free from cellular and serum components by:

(i) microfiltration to remove cell debris,

(ii) tangential flow ultrafiltration to remove serum components,

(iii) gel filtration to further remove serum components, and

(vi) ion-exchange chromatography to additionally remove serum components;

inactivating said purified virus with an inactivating agent selected from the group consisting of β-propiolactone, a non-ionic detergent which is n-octyl-α-D-glucopyranoside or n-octyl-β-D-glucopyranoside, and ascorbic acid, to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

15. A method of immunizing a host against disease caused by respiratory syncytial virus, which comprises administering to the host an effective amount of the vaccine composition of claim 1.

16. The method of claim 15 wherein said host is selected from infants, young children, pregnant women, women of child-bearing age, elderly individuals, immunocompromised individuals and susceptible persons.